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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/813,781	03/07/97	WEIDANZ	J 46745

EXAMINER

HM22/0310

LUBET,M

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/813,781	Applicant(s) Weidanz et al.
	Examiner Lubet	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Dec. 27. 1999*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4, 6-9, 13-15, and 18-74* is/are pending in the application.

Of the above, claim(s) *3, 9, 13, 15, 21-60, 62-64, 66, 68, and 70* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4, 6-8, 14, 18-20, 61, 65, 67, 69, and 71-74* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This office action is in response to Paper 21 filed Dec. 27, 1999.

2. Paper 21 added claims labeled claim 68-73. However, amendment filed Jan 4, 1998 added claims 60-68. The newly added claims in Paper 21 have renumbered under Rule 1.26 as claims 69-74, respectively. Claims 1-4, 6-9, 13, 14, 15, 18-68 and newly added claims 69-74 are pending. A species election of a soluble fusion protein comprising V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein was made in Paper 16. Claims 21-59 and 68 remain withdrawn from consideration as drawn to the non-elected invention. Claims 3, 9, 13, 15, 60, 62 , 63, 64 and 66 are drawn to non-elected species of invention and remain withdrawn from consideration. Newly added claim 70 is not drawn to the elected species of invention because the claimed fusion protein comprises Cα region component. Claim 70 is withdrawn from consideration as drawn to the non-elected species of the invention. Claims 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65, 67 and newly added claims 69 and 71- 74 are under examination as they read upon the elected species of TCR-bacteriophage coat protein fusion protein IE fusion protein comprising in sequence a V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein.

3. Rejections under 35 USC 112 first paragraph.

A. (maintained) Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The soluble TCR wherein the TCR comprises a human Cβ chain fragment claimed in Claim 20 has no clear support in the specification and the claims as originally filed. The specification and claims as originally filed disclose that the TCR fusion protein may be humanized, IE contain human TCR sequences, but does not specify that the human TCR sequences are derived from the constant domain of the beta chain. The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification to include fusion proteins wherein the Vβ region of the fusion chain is derived from non-human (IE murine) TCR fused to Cβ region derived from human TCR.

If applicants disagree, applicant should present a detailed analysis by point to page and line number as to why the claimed subject matter has clear support in the specification.
--The rejection set forth supra is maintained because Applicant has not specifically pointed out support for the sc TCR including a human Cβ chain fragment. Applicant's response that support for the specific limitation "TCR includes a human Cβ chain fragment" is found on pages 17, 18-19 and 21-42 is not persuasive because Examiner can not find support for this specific limitation. Examiner agrees that the specification discloses that the scTCR can be derived from human TCR, however, this is not support for the limitation wherein the scTCR includes a human Cβ chain since this limitation opens up the claim language to encompass hybrid scTCR wherein the alpha chain and/or Vβ components are not derived from the same sources, IE scTCR in which the alpha chain and Vβ sequences are derived from murine TCR and the Vβ components are derived from human TCR.

B. (new, necessitated by amendment) Claim 69 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The soluble TCR wherein the TCR V-α and Vβ region are each individually about 200-400 amino acids in length has no clear support in the specification and the claims as originally filed. The specification and claims as originally filed disclose that TCR V-α **and** Vβ region of the scTCR are about 200-400 amino acids in length (see page 14 in particular) (emphasis added by Examiner). Thus the specification discloses that the V-α and Vβ region are together about 200-400 in length and does not disclose that each region is 200-400 amino acids in length. It is noted that the intact TCR β-chain is 291 amino acids in length. The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicant should present a detailed analysis by pointing to page and line number as to why the claimed subject matter has clear support in the specification.

4. Claims 61, 65, 67 and 69 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The rejection of Claims 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65 and 67 under 35 U.S.C. § 112, second paragraph set forth in the previous office action is withdrawn in view of the amendment to the claims.

B. (NEW, necessitated by amendment) In claim 69 it is unclear what the fusion protein comprises. Claim 69 claims a fusion protein in which the V-α and Vβ region are individually 200-400 amino acids in length. The V-region of the beta chain is only 109 amino acids in length and the intact β-chain is 291 amino acids in length. It is unclear how a sequence of Vβ region or chain can be longer than the intact β chain.

5. (withdrawn) Claims 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65, 67 are rejected under 35 U.S.C. 112 first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Reasons are set forth below.

The claims are drawn to a soluble fusion protein comprising a Vα chain -peptide linker-Vβ - bacteriophage protein in which the fusion protein comprises an antigen binding pocket. The claims are enabled only for fusion proteins which comprise a Cβ region. TCR fusion proteins which do not comprise the Cβ region would not expected to comprise an antigen binding pocket since WO 96/18105 further teach that TCR fusion proteins which do not contain the Cβ do not fold into the native conformation (see page 30, line through page 31, line 31, in particular).
--The rejection is withdrawn in view of the amendment to the claims.

6. (maintained) Claims 1, 2, 4, 6-8, 14, 18, 19, 20 61, 65, 67, 69 and 71-74 are rejected under 35 U.S.C. 103(a) as unpatentable over WO 96/18105 (issued 13 June 1996) in view of Barbas US 5,759,817 (filed Jan. 27, 1992), Onda et al. (Molecular Immunology 32:1387, 1995), and Huse et al. J. Immunology 149:3914, 1992

Claims 1, 2, 4, 7-8, 14, 18, 19, 20, 61 and 67 are drawn to a soluble fusion protein comprising in sequence V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein. Claims 6 and 65 are

drawn to fusion protein further comprising a protein tag. In claim 65 the protein tag is covalently linked to the C-terminus of the Cβ fragment and the N-terminus of the VIII protein. Claims 69 and 71-74 are drawn to species of the fusion protein (IE ones in which Cβ is about 50 to 126 amino acids in length).

WO 96/18105 teaches a single chain T cell receptor which specifically binds to peptide ligand (see abstract). WO 96/18105 further teaches one embodiment of human single chain TCR in which C-terminus of Vα domain is linked to N-terminus of Vβ chain via a 15 amino acid residue flexible amino acid liner and the C-terminus of the Vβ chain is linked to the beta chain constant domain (see pages 3 and 5 and Figure 1, in particular). In one embodiment the C terminus of Vβ chain is linked to a alkaline phosphatase (PI) protein tag (see Figure 1, in particular). WO 96/18105 also teaches that the order of the domains within the single chain TCR is interchangeable (see page 5, in particular). WO 96/18105 also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. WO 96/18105 also teach that a preferred embodiments of linkers are composed of amino acids which tend to increase solubility in aqueous solution (see page 8, lines 1-25, in particular). WO 96/18105 further teach that the TCR fusion protein comprising V-α-peptide linker-Vβ-Cβ fusion protein can be linked to additional segments which do not interfere with the essential properties of the encoded molecule (see page 8, lines 5-8, and page 9, lines 1-9, in particular). WO 96/18105 disclose that the TCR fusion protein can bind antigenic protein, thus teaching that the TCR fusion protein comprises an antigen binding pocket. WP 96/18105 exemplifies a TCR fusion protein comprising V-α-peptide linker-Vβ-Cβ-linked to GPI anchor and expression of such a fusion protein in a transfected eukaryotic cell (see page 17, lines 13-31, in particular). WO 96/18105 further disclose that the soluble form of TCR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific phospholipase C (PI-PLC) (see page 17, lines 23-24, in particular). WO 96/18105 also teaches expression of V-α-peptide linker-Vβ-Cβ TCR fusion protein in a bacterial cell system in which the N terminus of the Cβ region is linked to a histidine protein tag (see pages 26-30, in particular). WO 96/18105 further teach that such a protein was predominantly accumulated in the inclusion bodies but that the TCR fusion protein could be isolated in one-step nickel affinity chromatograph with a yield of 5-10 mg of TCR fusion protein per liter of bacteria culture. Additionally WO 96/18105 also disclose a scTCR in which comprises Vα-linker-Vβ-Cβ 0GPI in which the Cβ component consists of the β chain sequence ending right before the last cysteine (the sixth cysteine) (see page 21, lines 20-32, in particular). Such a fusion protein meets the claim limitation of claim 72. WO 96/18105 further teach that TCR fusion proteins which do not contain the Cβ do not fold into the native conformation (see page 30, line through page 31, line 31, in particular).

The scTCR disclosed by WO 96/18105 meet the length limitations of the Vα and Vβ region recited in claims 69, 70 and 71 since the term "about 200 to about 400" and "about 50-126" has been interpreted broadly to encompass the length of Vα and Vβ components of the scTCR taught by WO96/18105.

The W0 96/18105 further teaches that the single chain TCR may be derivatized by conjugation of group which does not alter the binding characteristics of the single chain TCR (see page 9, lines 2-20, in particular).

Thus WO 96/18105 teach a soluble fusion protein comprising a Vα-peptide linker-Vβ-Cβ-protein tag. WO 96/18105 does not teach a TCR fusion protein further comprising bacteriophage VIII coat protein.

However, Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see abstract and column 15, lines 27-28, in particular). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant(C) region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII (see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular. One embodiment of the invention is disclosed to be a fusion protein comprising in sequence a leader sequence-peptide linker-V region amino acid residue-peptide linker -phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). Thus Barbas discloses but does not exemplify a soluble fusion protein comprising a bacteriophage coat protein covalently linked to T cell receptor domains.

Onda et al .disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et al. also teach that TCR-bacteriophage coat protein fusion protein can be used

to study specific binding interactions of the TCR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular).

Huse et al. teach that fusion proteins comprising a single chain fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can recovered from culture medium or from the periplasmic space (see abstract).

Therefore it would have been obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TCR fusion protein comprising the Vα-peptide linker-Vβ-Cβ-protein tag component taught by WO 96/18105 linked to a bacteriophage VIII coat protein because Barbas et al. and Onda et al. teach TCR-bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities. One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TCR component or to use the protein to elicit anti-idiotypic antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Cα and Cβ region was derived from human TCR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TCR component of the protein.

--Applicant's response on pages 6-8 of Paper of Paper 21 and the Rule 131 declaration filed Dec. 27, 1999 have been considered but is not persuasive. Applicant urges that WO 96/18105 is not available as art in light of the declaration filed Dec. 27, 1999. Applicant states that the claimed fusion protein, a fusion protein comprising in sequence Vα- linker-Vβ-Cβ--bacteriophage coat VIII protein was reduced to practice before the publication date of WO96/18105 on June 13, 1996. The vector encoding sequence Vα- linker-Vβ-Cβ--bacteriophage coat VIII protein is pKC44 discussed in the declaration is the same as pKC44 in Example 2 (page 45) and Figure 2 of the instant specification. The Vα-Vβ-Cβ TCR encoded by pKC44 is derived from murine TCR specific for ovalbumin (see page 43 of the specification) and the Cβ component consists of 126 amino acids. The declaration is sufficient to establish that TCR fusion protein having the structural characteristics of the fusion protein claimed in claims 1, 2, 4, 7-8, 14, 19 67 and 71-72 were made before June 13, 1996. However, the 131 declaration filed Dec. 27, 1999 is insufficient to establish that the fusion protein claimed in claims 6 and 65 (comprise at least one protein tag), claims 18 (isolated from a cytotoxic T cell) , claim 19 (produced by cleaving one or more protein tags), claim 20 (comprises human Cβ), claim 69 (Vα and Vβ component are individually 200-400 amino acids in length) , claims 61 (comprises gene III protein), claim 73

(bacteriophage coat protein is gene III) and claim 74 (bacteriophage coat protein VIII is 40-50 amino acids) was reduced to practice prior to June 13, 1996 because the fusion protein encoded by pKC44 does not meet the claim limitations of claims 6, 18, 19, 20, 65, 69, 61, 73 and 74. Additionally there is no evidence of record that the TCR fusion protein encoded by pKC44 "effectively positions the Vα and Vβ region to form the antigen binding pocket." The specification and the declaration filed Dec. 27, 1999 are silent with regard to ability of the fusion protein encoded by pKC44 to form a binding pocket. Applicant could address the rejection of claims 1, 2, 4, 7-8, 14, 67 and 71-72 with regard to the ability of the fusion protein encoded by pKC44 to form a antigen binding pocket by filing evidence that the fusion protein binds the relevant antigen and/or stimulates T cells specific for the relevant antigen.

8. Examiner believes that all pertinent arguments have been addressed.

9 No claim is allowed. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet in Art Unit 1644 whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet in Art Unit 1644 whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973 The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet
March 13, 2000

Christina Chan
CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640